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EXAMINER

TON, THAIAN N

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/080,713	Applicant(s) COLMAN ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 January 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 62,63,65,66,73,75-79,82,88-90,99,100,102-110,113,119-125,131,133-137 and 139-148 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,73,75-79,82,88-90,99,100,102-110,113,119-125,131,133-137 and 139-148.

DETAILED ACTION

Applicants' Amendment and Response, filed 1/20/11 has been entered. Claims 62, 90, 131, 133, 142, 144 are amended; claims 87, 118, 138, 149-152 are cancelled; claims 62, 63, 65, 66, 73, 75-79, 82, 88-90, 99, 100, 102-110, 113, 119-125, 131, 133-137, 139-148 are pending and under current examination.

Enablement

The prior rejection of claims 62, 63, 65, 66, 73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133-152 under 35 U.S.C. 112, first paragraph, is withdrawn in view of Applicants' amendment to the claims, which now recite the production of a non-human transgenic mammal, and additionally, recite that the modification of the endogenous locus is by homologous recombination.

Claim Rejections - 35 USC § 112

The prior rejection of claims 87, 118, 138 is rendered moot in view of the cancellation of the claims.

The prior rejection of claims 142, 143 and 146 is withdrawn in view of Applicants' amendment to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 62, 63, 65, 66, 75, 76, 82, 88-90, 99, 100, 106, 113, 119-122, 131, 133-136, 140, stand rejected under 35 U.S.C. 102(b) as anticipated by Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS).

Applicants' Arguments. Applicants argue that the Examiner could not have responded to all of Applicant's arguments in the prior Office action because the argument that the non-enablement of Campbell does not dictate the non-enablement of the present invention was the focus of the response of the Response dated June 24, 2010. Applicants argue that the non-enablement of a prior art reference doesn't dictate the non-enablement of the present invention – to the extent that those two references differ in a meaningful way. Applicants point to the *Wands* factors, and argue that at least two of these factors differ between i) the level of ordinary skill and ii) the existence of working examples. While those differences are not reflected in the claims, it is hard to imagine how they could be – they are important criteria for determining enablement under *Wands*. Nor does enablement dictate, as the Examiner seems to conclude, that Applicants must amend their claims to be distinguished from the prior art, or put more specifically, recite different or new steps, which seems to be the Examiner's sole focus. The closest relevant factor under *Wands* would appear to be the amount of disclosure – to the extent that additional disclosure might be assumed to provide additional or different steps. But that one factor under *Wands* alone is not determinative, while the Examiner appears to discount those factors under *Wands* that do benefit the present invention as compared to the prior art – and break the connection between

the two the Examiner is using to drive the present 102(b) rejection. See pages 9-10. Applicants state that they understand that the present rejection is prior art-based, and submit that Campbell is non-enabled. Applicants state that all prior art enablement rejections have been overcome. See p. 11 of the Response.

Response to Arguments. These arguments have been considered but are not persuasive. Firstly, the Examiner asserts that all prior arguments have been fully addressed. The Examiner has addressed the issues that Applicants have brought up regarding the non-enablement of Campbell versus the enablement of the instant invention in the prior Office action. Applicants do not point to any particular section or argument that the Examiner has not addressed. Simply because Applicants' arguments are not persuasive, or have not been resolved, does not mean that the Examiner has not addressed them. As reiterated from prior Office actions, Campbell teach methods of modifying the exact same cell type (a fibroblast), to produce the same result (a non-human transgenic animal). The Examiner further responds that Applicants have not pointed to the *Wands* factors that the Examiner has not considered, and how these would result in the non-enablement of Campbell. There is no requirement for the Examiner to analyze Campbell in view of 112, 1st, enablement, which is necessary for the enablement of the examined invention, not the cited prior art.

Pertinent to this issue, it is noted that in a recent decision, *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297 (Fed. Cir. 2005), the court indicated:

The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112. In *In re Hafner*, 410 F.2d 1403 [[161 USPQ 783](http://iplaw.bna.com/iplw/5000/link_res.adp?fedfid=3683261&fname=uspq_161_783&vname=ipqcases2)] (CCPA 1969), the court stated that "a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim." *Id.* at 1405; see *Schoenwald*, 964 F.2d at 1124; *In re Samour*, 571 F.2d 559, 563-64 [[197 USPQ 1](http://iplaw.bna.com/iplw/5000/link_res.adp?fedfid=3683261&fname=uspq_197_1&vname=ipqcases2)] (CCPA 1978). The reason is that section 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such

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requirement as to an anticipatory disclosure." *Hafner*, 410 F.2d at 1405; see 1 Donald S. Chisum, Chisum on Patents §3.04[1][c] (2002); see also *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349-52 [64 USPQ2d 1202] (http://iplaw.bna.com/iplw/5000/link_res.adp?fedfid=3683261&fname=uspq2d_64_1202&vname=ippqcases2) (Fed. Cir. 2001) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method).

Since *Hafner*, this court has continued to recognize that a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102. See *Schoenwald*, 964 F.2d at 1124 ("it is beyond argument that no utility need be disclosed for a reference to be anticipatory of a claim"); *In re Donohue*, 632 F.2d 123, 126 n.6 [207 USPQ 196] (http://iplaw.bna.com/iplw/5000/link_res.adp?fedfid=3683261&fname=uspq_207_196&vname=ippqcases2) (CCPA 1980) ("proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. §102(b)"), citing *In re Samour*, 571 F.2d at 563-64; see also Application of *Lukach*, 442 F.2d 967, 969 [169 USPQ 795] (http://iplaw.bna.com/iplw/5000/link_res.adp?fedfid=3683261&fname=uspq_169_795&vname=ippqcases2) (CCPA 1971) (recognizing that there are "anomalies between the requirements for claim-anticipating disclosures and for claim-supporting disclosures" and citing *Hafner* as an example).

Also, see *Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc.*, 81 USPQ2d 1001 (Fed. Cir. 2006).

Therefore, all of the cited case law supports §102 does not require the same standard of enablement as 112, 1st. Additionally, as clear from above, the courts have recognized that proof of utility is not a prerequisite to the availability of a prior art reference under 35 USC §102(b). Applicants have not established any convincing reason as to why Campbell does not anticipate the claims; therefore the rejection is maintained.

In the instant case, because Campbell teaches each and every method step required by the claims, it must be enabled, absent specific evidence to the contrary. Finally, the proof of efficacy is not required for Campbell to be enabling for the purposes of anticipation. Thus, Applicants have not met the burden as to how the instant invention is distinguished from Campbell's methods, such that it would be clear that Campbell's methods are not enabled, or that Campbell does not anticipate the claimed methods. Applicants have not shown how Campbell's methods would be considered inoperative, given that Campbell teaches the same method steps to produce the same result as the instant invention.

Additionally, as stated previously, a working example is not a requirement for a piece of art under 102 to be considered non-anticipatory. Campbell teaches the

same method steps as that which is instantly claimed. Thus, the ordinarily skilled artisan, following Campbell at the time of filing, would have been able to achieve the invention as claimed. The MPEP at §2138.05(a) clearly shows that reduction to practice does not require the disclosure to produce a particular product, but to provide a method of doing so: "Reduction to practice may be an actual reduction or a constructive reduction to practice which occurs when a patent application on the claimed invention is filed. The filing of a patent application serves as conception and constructive reduction to practice of the subject matter described in the application. Thus the inventor need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application. *Hyatt v. Boone*, 146 F.3d 1348, 1352, 47 USPQ2d 1128, 1130 (Fed. Cir. 1998)."

Rejection

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene knock ins and other gene modifications, and optionally the cells may be transfected with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines 10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic

modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Campbell teaches that the donor nucleus is genetically modified, and that this nucleus may contain one or more transgenes (p. 7, lines 1-5).

Claims 62, 63, 65, 66, 75, 76, 82, 88-90, 99, 100, 106, 113, 119-122, 131, 133-136, 140 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 6,147,276 (Issued November 14, 2006, filed February 19, 1997).

Applicants provide the same arguments that are provided for the rejection above, namely, that this reference is not enabled and therefore may not be used as a 102(e). The Examiner has provided arguments and evidence as to why this reference is enabled and anticipates the claimed invention. As noted above, this reference teaches the exact same method steps, starting product, and ending product as the instant invention. Therefore, this reference anticipates the claimed invention.

The Examiner further notes that Applicants previously argued regarding both references under the same heading (see pages 8-11). The Examiner addressed all of Applicants' arguments regarding these references. Therefore, these arguments were fully considered and the Examiner's remarks fully responsive.

Rejection

Regarding claims 62, 90, 131, 133, the '276 patent teaches methods of nuclear transfer to produce transgenic mammals (Abstract). The '276 patent teaches that donor cells can be fibroblasts (col. 4, lines 10-11). The '276 patent teaches producing cloned animals by transferring the donor cell nucleus into an enucleated metaphase

II oocyte (col. 5, lines 58+), the activation of the resultant NT unit (col. 6, lines 63+) and developing a cloned animal from the embryo (col. 7, lines 35-44). The '276 patent teaches that transgenic animals can be produced by the claimed methods (col. 3, lines 16-20). The '276 patent teaches specific methods of modifying endogenous genes, including deletion of specific endogenous genes. These methods require specific targeting, which is only accomplished by homologous recombination.

Regarding claim 63, the '276 patent teaches producing sheep, goat, camels, pigs (col. 3, lines 6-9).

Regarding claims 65, 66, 99, 100, 136 the '276 patent teaches that endogenous genes can be deleted, duplicated, activated or modified (col. 3, lines 43-54 and col. 10, lines 43-49).

Regarding claims 75, 76, 106 the '276 patent teaches that transgenesis may be employed with selectable markers (col. 10, lines 47-49).

Regarding claims 82, 113, the '276 patent teaches that the genetic modification can be produced by lipofection (col. 4, lines 63-64).

Regarding claim 87 the '276 patent teaches utilizing fibroblasts as donor cells (col. 4, lines 10-11).

Regarding claims 88, 89, 119, 120, the '276 document teaches inducing quiescence and arrest the cells in G0 phase of the cell cycle by serum starvation (col. 9, lines 39-41; col. 10, lines 17-18).

Regarding claims 121, 122, the '276 document teaches transfection by electroporation (col. 3, lines 60-64).

Regarding claims 134 and 140, the '276 document teaches that the transgenic donor nucleus may contain one or more transgenes (col. 4, lines 55+).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 62, 63, 65, 66, 75-79, 82, 88-90, 99, 100, 106-110, 113, 119-124, 131, 133 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of d'Apice *et al.* (**U.S. Pat. No.** 5,849,991 published December 15, 1998).

Applicants' Arguments. Applicants argue that Campbell fails as a reference under §103 for the same reasons as it fails under §102, because it is non-enabled.

Response to Arguments. These arguments have been fully addressed above; the rejection is maintained.

Rejection

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene knock ins and other gene modifications, and optionally the cells may be transfected with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines

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10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Although Campbell do not specifically teach knockout of the alpha 1-3 galactosyltransferase gene, prior to the time of the claimed invention, d'Apice teach methods for reduction or elimination of the hyperacute rejection response in human, in particular, by producing knockout animals which lack or have reduced alpha 1-3 galactosyltransferase activity (see col., 1, Field of Invention). They specifically teach the porcine sequence (Figure 4), but teach that variations of these sequences can readily be generated by the skilled artisan (col. 2-3, bridging ¶). They teach generation of mammals lacking alpha 1-3 galactosyltransferase (col. 4, lines 54-60), wherein both copies of the gene are inactivated (col. 5, lines 1-2). d'Apice further teach that their targeting construct can contain a selectable marker, including the gene imparting resistance to the antibiotic G418 (col. 13, lines 20-22). They teach any marker that is suitable for inclusion in a knockout marker can be used (col. 13, lines 26-27). They specifically teach that GFP can be used in a construct, in order to detect gene targeting events. Col. 59, lines 5-9 and lines 23-33.

Accordingly, in view of the combined teachings of Campbell and d'Apice, it would have been obvious for one of skill in the art to modify the teachings of Campbell, to specifically inactivate the alpha 1-3 galactosyltransferase gene in a somatic cell, and to use this somatic cell in methods of nuclear transfer in order to produce an animal, wherein the alpha 1-3 galactosyltransferase gene has been inactivated, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification, given

Campbell's teachings for increasing efficiency of producing transgenic animals, and further, given d'Apice's teachings for the need in the art to produce animals whose organs can then be used for xenotransplantation, wherein the knockout of the alpha 1-3 galactosyltransferase gene reduces or eliminates the hyperacute rejection response. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by d'Apice, and instantly claimed, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 73, 75-77, 82, 88-90, 99, 100, 102, 105-108, 113, 119-122, 125, 131, 133, 144, 145 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Kucherlapati *et al.* (**WO 94/02602**, published February 3, 1994).

Applicants provide the same arguments with regard to Campbell. These arguments are addressed above; the rejection is maintained.

Rejection

Campbell is described above. Campbell does not specifically teach inactivation of an endogenous immunoglobulin gene. However, prior to the time of the claimed invention, Kuncherlapati teach the production of non-human mammals with inactivated endogenous Ig loci (see Abstract). In particular, Kuncherlapati teach an art-recognized interest in producing xenogeneic human monoclonal antibodies using transgenic animals (p. 2, lines 23-31). They teach methods of knocking out of the endogenous Ig loci and knocking in of human Ig (p. 6, lines 6-12; p. 10, lines 10-12). Kuncherlapati teach knockout of the endogenous Ig in mouse ES

cells, they suggest producing any mammalian host using their methods (p. 10, lines 1-2, pages 16-17). Additionally, Kuncherlapati teach that their targeting constructs can contain various marker genes, including those which confer G418 resistance (p. 16, lines 34-36). Kuncherlapati further teach that the targeting construct may include a replication system, including a promoter (p. 18, line 8).

Accordingly, given the combined teachings of Campbell and Kuncherlapati, it would have been obvious for one of ordinary skill in the art to use the technology of Campbell, and inactivate an endogenous Ig gene in a somatic cell, with a reasonable expectation of success. Although Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, Campbell provides the teachings and suggestion to use a somatic cell, and then use the modified somatic cell in methods of NT to produce transgenic animals. One of ordinary skill in the art would have been sufficiently motivated to knockout an endogenous Ig gene, as supported by Kuncherlapati, who teach that it is an art-recognized goal to produce xenogeneic specific binding proteins, such as human monoclonal antibodies (p. 2, lines 23-32) by production of transgenic animals. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by Kuncherlapati, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

With regard to claim 73, this claim only requires that the promoter directs expression of one gene in fibroblast cells. This does not exclude a promoter that directs expression in all cells, such as a ubiquitously expressed promoter.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 75, 76, 82, 88-90, 99, 100, 102, 104, 106, 113, 119-122, 131, 133-136, 144, 145, 147 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of US Pat. No. 6,013,857 (Filed June 5, 1995, Issued January 11, 2000).

Applicants provide the same arguments with regard to Campbell. These arguments are addressed above; the rejection is maintained.

Rejection

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome, wherein the promoter is a milk promoter. However, prior to the time of the claimed invention, the '857 patent discusses producing transgenic bovines for producing recombinant polypeptides in milk (Abstract). Particularly, they teach using endogenous milk regulation (*i.e.*, promoter) sequences (col. 8-9, bridging ¶).

Accordingly, it would have been obvious for one of ordinary skill in the art, to modify the methods, as taught by Campbell, to place a transgene of interest adjacent to an endogenous promoter, such as a milk promoter, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification, in view of the '857 patent which teaches that these methods would be used in order to produce recombinant polypeptides of interest from transgenic bovine species and isolate the recombinant polypeptide from milk (Abstract).ok

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 75, 76, 82, 88-90, 99, 100, 102, 103, 106, 113, 119-122, 131, 133, 144, 145, 148 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Bedalov (**Journal of Biol. Chem.**, 269(7): 4903-4909, 1994) when taken with Rossert (**The J. of Cell Biol.** 129(5): 1421-1432, 1995).

Applicants provide the same arguments regarding Campbell. The Examiner has addressed these arguments above.

Rejection

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome wherein the promoter is a collagen gene promoter. However, prior to the time of the claimed invention, Bedalov discuss a transgene containing the COL1A1 promoter fused to a reporter gene and discuss its expression in a variety of mesenchymal cell types, including fibroblasts, osteoblasts and odontoblasts (see p. 4903, 1st col., 1st ¶). Bedalov teaches that transgenic mice which have ~3.5 kb of COL1A1 upstream promoter have strong expression of the reporter gene in high collagen producing tissues, such as tendon, bone and skin (p. 4903, col. 2, first full ¶). Bedalov teach that the COL1A1 construct, including the COL1A1 promoter confers tissue-specific expression in transgenic animals, with no aberrant expression (see pp. 4908-4909, bridging sentence). Bedalov suggest that making transgenic animals with genome-integrated transgenes would allow for further analysis of endogenous gene expression and would provide a model that is more biologically representative for the interaction of trans-acting factors with the sequences in the promoter (p. 4909, 1st full ¶, last sentence).

Accordingly, it would have been obvious for one of ordinary skill in the art, to utilize the teachings to make a transgenic, gene targeted animal, by nuclear transfer, as taught by Campbell, and specifically target a transgene under the expression of a collagen promoter, such as that taught by Bedalov, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Bedalov's teachings, which show an art-recognized need to further analyze the expression of the COL1A1 promoter in transgenic animals, and additionally, in view of Rossert, who teach that the precise sequences responsible for the lineage-specific expression of the collagen

promoter have not been defined (p. 1421, col. 2, last bridging ¶). Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS) when taken with US Pat. No. 7,321,075 B2 (Campbell *et al.*, published January 22, 2008).

Applicants provide the same arguments regarding Campbell. The Examiner has addressed these arguments above.

Rejection

Campbell is described above. They do not specifically teach that the cells from the embryo are further used for rounds of NT, wherein additional genetic modifications are introduced prior to further rounds of NT. However, prior to the time of filing of the claimed invention, the '075 patent teaches methods of nuclear transfer to produce transgenic animals, and specifically teach that serial nuclear transfer can be used. In particular, they state, "It may be possible for increased yields of viable embryos to be achieved by means of the present invention by clonal expansion of donors and/or if use is made of the process of serial (nuclear) transfer." See col. 8, lines 4-8 and claim 1. Thus, the '075 patent provides clear guidance for using the cells of the embryos for further rounds of NT. Additionally, the '075 patent teaches the production of transgenic animals by the isolation of diploid donor cells, transgenesis, embryo reconstitution by NT, culturing of the NT embryo to blastocyst stage, and transfer to a final recipient (col. 10, lines 31+). Particularly, the '075 patent teaches that the donor nucleus may contain one or more transgenes and that this genetic modification may take place prior to nuclear transfer and embryo reconstruction (col. 4, lines 4-8).

Accordingly, it would have been obvious to the skilled artisan, to modify the NT techniques taught by Campbell, to include serial nuclear transfer, wherein cells

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of the NT embryo are used for further rounds of NT, with a reasonable expectation of success. One of skill in the art would have been motivated to make this modification in view of the '075 patent's suggestion that serial nuclear transfer may provide for increased yields of viable embryos. Additionally, one of skill in the art would recognize that the '075 patent's teachings provide guidance to make genetic modifications prior to further rounds of NT. In particular, the '075 patent teaches that genetic modifications occur prior to NT and embryo reconstruction (col. 4, lines 4-8) and further, that NT embryos that are used in serial NT provide the donor nucleus. Thus, it would have been obvious for one of ordinary skill in the art to utilize the donor cell/nucleus, isolated from a NT embryo, and add further genetic modifications prior to another round of NT, with a reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 134-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS) when taken with US Pat. No. 7,329,796 B2 (Campbell *et al.*, Published February 12, 2008).

Campbell is described above. They do not specifically teach using cells from the NT embryo/fetus or adult for further rounds of NT. However, prior to the time of filing of the claimed invention, the '796 patent teaches methods producing animal embryos by NT (Abstract). Particularly, they teach methods of preparing ungulate animals by forming a first embryo by NT, isolating cells from the first embryo and forming a second embryo by NT, transferring the second embryo to produce fetus that undergoes full fetal development to produce an ungulate animal (claim 1). Thus, the '796 patent provides guidance for serial nuclear transfer. The '796 patent teaches methods of producing transgenic animals that contain one or more

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transgenes, and that the genetic modification takes place prior to NT and embryo reconstruction (col. 3, lines 55+). The '796 patent teaches that serial rounds of nuclear transfer may increase the yields of viable embryos (col. 8, lines 50+). The '796 document teaches using adult cells or fetal cells as donor cells (claims 7, 17, 19, 27, 28, 29).

Accordingly, it would have been obvious to the skilled artisan, given the combined teachings of Campbell and the '796 patent, to modify the teachings of Campbell, and utilize multiple rounds of NT, with a reasonable expectation of success. One of ordinary skill in the art, reading the '796 patent would recognize that the source of donor cell can be isolated from embryonic, fetal or adult tissue, and could be used from the animals produced by NT. Additionally, one of skill in the art the '796 patent's teachings provide guidance to make genetic modifications prior to further rounds of NT. In particular, the '075 patent teaches that genetic modifications occur prior to NT and embryo reconstruction (col. 3, lines 55+). Thus, given the combined teachings, it would have been obvious to the skilled artisan that 1) genetic modifications could be performed prior to a subsequent round of NT; and 2) that utilizing tissue from a cloned embryo/fetus or adult animal would provide an embryonic, fetal or adult donor cell for NT. These steps are all known and taught in the cited art. It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A)

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Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.”

In the instant case, at least rationale B), C) and D) apply to the instant invention. That is, one of skill in the art recognized that genetic modification must take place prior to nuclear transfer. Additionally, the art provides guidance to show that embryonic, fetal or adult donor cells may be for nuclear transfer to produce cloned animals. Thus, one of skill in the art could readily use cells produced by nuclear transfer, either from an embryo, fetus or adult cloned animal for subsequent genetic modifications and rounds of NT. Additionally, although not explicitly taught that the genetic modifications can occur either simultaneously, subsequently or sequentially, the combined art provides guidance to produce transgenic animals by NT that contain multiple genetic modifications. It would have been obvious to one of skill in the art to introduce transgenes into a donor cell by any of the claimed ways, because transfecting cells was a known technique recognized as part of the ordinary capabilities of one skilled in the art, and additionally, a finite number of identified solutions - either the addition of the transgenes simultaneously, sequentially or subsequently – would provide a

reasonable expectation of success to producing a gene targeted donor cell with specific gene targeted modifications.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 144 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell (WO 97/07669, published 6 March 1997, Applicants' IDS) when taken with Salminen *et al* (**Dev. Dynamics**, 212: 326-333, 1998).

Applicants provide the same arguments regarding Campbell. The Examiner has addressed these arguments above.

Rejection

Campbell is described above. However, they do not specifically teach that the modification of the nuclear genome places a transgene at a site which places the transgene under the control of an endogenous regulatory region (claim 144); and specifically that the endogenous regulatory region comprises a polyadenylation site.

However, prior to the time of filing, Salminen teach methods of producing a PolyA trap vector that is driven by a constitutive promoter that integrates with high frequency and traps genes with very different expression patterns (Abstract).

Accordingly, in view of the combined teachings, it would have been obvious to modify the techniques taught by Campbell, and utilize a poly A trap vector, such as that taught by Salminen, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification in order to produce transgenic animals which could be used identify developmentally important genes, and study expression patterns of genes trapped *in vivo*.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

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Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/

Primary Examiner, Art Unit 1632